Summary of vaccine safety studies of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and their infants

Study design	Study period*	Vaccine	Population	Findings/Conclusions
Vaccine Adverse Events Reporting System				
Spontaneous system	2005–2010	Tdap	132 pregnant women or their infants	No unusual or unexpected pattern of maternal, infant or fetal adverse events. (*1*)
Spontaneous system	2011–2015	Tdap	392 pregnant women or their infants	No new unexpected vaccine safety concerns noted among pregnant women who received Tdap. (*2*)
Spontaneous system	1990–2014	Tdap, Td, 4vHPV, Influenza, HepB, MMR, VAR	3389 pregnancy reports	31 reports of chorioamnionitis following receipt of any vaccines, representing 1% of pregnancy reports to VAERS; 26% reported Tdap vaccine administered; Majority of reports had at least one risk factor for chorioamnionitis. (*3*)
Vaccine Safety Datalink				
Retrospective cohort; 7 sites	2007–2013	Tdap	29,155 pregnant women	No increased risk of medically attended acute adverse events (fever, allergy, and local reactions) or adverse birth outcomes (small for gestational age, preterm delivery, and low birth weight) related to timing since prior tetanus-containing vaccination (i.e., less than 2 years before, 2 to 5 years before, and more than 5 years before). (*4*)
Retrospective cohort; 7 sites	2007–2013	Tdap, Influenza	Pregnant women: 8,464 concomitantly 28,380 sequentially	No statistically significant increased risk of fever or any medically attended acute adverse event in pregnant women concomitantly administered vaccine compared with sequentially administered vaccine; No differences in both groups in pregnancy outcomes (e.g., small for gestational age, low birth weight, preterm delivery). (*5*)
Retrospective cohort; 7 sites	2007–2013	Tdap	Pregnant women: 41,654 vaccinated; 282,809 unvaccinated	Tdap vaccination during pregnancy was not associated with increased risk for birth defects, including microcephaly, among live birth offspring. (*6*)
Retrospective cohort; 7 sites	2007–2013	Tdap	Pregnant women: 53,885 vaccinated; 109,253 matched unvaccinated	No increased risks for acute neurologic events, proteinuria, thrombocytopenia or venous thromboembolism following maternal vaccination; No increased risk for fever, malaise, allergic, local and other reactions. (*7*)
Retrospective cohort; 2 sites	2010–2012	Tdap	Pregnant women: 26,229 vaccinated; 97,265 unvaccinated	Receipt of Tdap during pregnancy was not associated with increased risk of hypertensive disorders of pregnancy or preterm or SGA birth;

				Small but statistically significant increased risk of chorioamnionitis diagnosis observed; but did not observe increased risk of preterm birth, a major sequela of chorioamnionitis. (*8*)
Other Studies				
Tdap/Td exposure during phase 3 randomized controlled trial	2001–2002	Tdap, Td	Pregnant women: 23 received Tdap; 7 received Td	During trial participation, 30 women became pregnant 1 or more times; Tdap group: 5 spontaneous abortion and 2 preterm births; Td group: 1 therapeutic abortion and 2 preterm births; For Tdap and Td groups, 23 newborns (including 4 preterm births) reported normal. (*9*)
Tdap exposure during mass vaccination campaign	2006	Tdap	16 pregnant women	All gave birth to full-term infants who had normal newborn evaluations. (*10*)
Retrospective cohort	2005–2009	Tdap	From 162,448 pregnancies: 138 vaccinated; 552 unvaccinated (randomly selected controls)	Tdap administration occurred most often in the first trimester as prophylaxis following trauma; Incidence of spontaneous or elective abortions no greater in vaccinated than unvaccinated; No significant differences in preterm delivery, small for gestational age, or birth weight between groups; No increase in adverse outcomes noted among infants from vaccinated group compared with unvaccinated group. (*11*)
Sanofi Pasteur Vaccine Pregnancy Registry; prospective reports	2005–2011	Tdap	480 pregnant women	Data from registry do not raise concern for maternal or infant health Adverse event: 27 (6%) serious adverse events, 33 (7%) non-serious adverse events, 262 (55%) no adverse events, and 158 (33%) did not report an adverse event; Birth outcome: 93 (19%) term deliveries, 7 (2%) preterm deliveries, 1 (<1%) very preterm delivery with no congenital anomaly, 2 (<1%) elective abortions, 16 (3%) spontaneous abortions, 123 (26%) lost to follow-up and 238 (50%) awaiting pregnancy outcome. (*12*)
Phase 1-2 clinical trial	2008–2012	Tdap, Placebo (saline)	Pregnant women: 33 received Tdap; 15 received placebo	No increased risk of adverse events was observed among women who received Tdap or their infants; Growth and development were similar in both infant groups. (*13*)
Retrospective cohort; public hospital	2012–2014	Tdap	Pregnant women: 1,109 vaccinated; 650 unvaccinated	No increased risk associated with Tdap administration during pregnancy for maternal outcomes (i.e., chorioamnionitis, postpartum endometritis, preterm delivery, preterm premature rupture of membranes and induced labor) or infant outcomes (i.e., low birth weight, very low birth weight, small for gestational age, 5-minute Apgar score, birth defects, and neonatal intensive care unit admission). (*14*)

Retrospective cohort	2013–2014	Tdap	Pregnant women: 7,152 vaccinated; 226 unvaccinated	No difference in stillbirths, major malformations, chorioamnionitis, 5-minute Apgar score, cord blood pH, or rates of neonatal complications; No increased risk for preterm birth, small for gestational age, and length of neonatal hospitalization; No difference in neonatal outcomes between women given at least two doses of Tdap in past 5 years and those who received a single dose. (*15*)
Studies from Other Countries				
Clinical trial Mexico	2011–2014	Tdap, Placebo (saline)	Pregnant women: 90 received Tdap 81 received placebo	Most common reaction among Tdap and placebo groups was mild local pain in 22% and 21%, respectively. (*16*)
Retrospective cohort United Kingdom	2012–2013	Tdap	20,074 pregnant women who received Tdap compared to matched historical unvaccinated control group	No evidence of increased risk of stillbirth, maternal or neonatal death, pre-eclampsia or eclampsia, haemorrhage, fetal distress, uterine rupture, placenta or vasa previa, caesarean delivery, low birth weight, or neonatal renal failure; No evidence vaccination accelerated time to delivery compared with historical controls. (*17*)
Prospective cohort Belgium	2012–2014	Tdap	Pregnant women: 57 vaccinated; 42 unvaccinated	Reported adverse events within this study (73.7% showed mild to moderate injection site pain and swelling) did not differ from the expected side effects described in vaccine package insert; Among infants, no unexpected risk pattern or congenital disorders detected. (*18*)
Prospective observational New Zealand	2012–2014	Tdap	793 pregnant women	Injection site reactions common, minor and self-limiting; systemic reactions uncommon; Vaccination with Tdap well tolerated; no severe adverse events likely caused by vaccine. (*19*)
Summary of maternal vaccination program Argentina	2012–2014	Tdap	20 pregnancy reports	7 reports of mild reaction following receipt of Tdap; 12 reports due to program errors (i.e., Tdap administered before recommended gestational age or revaccinated with Tdap); No reported serious or fatal events. (*20*)
Prospective observational New Zealand	2012–2014	Tdap	408 infants whose mothers received Tdap during pregnancy	No significant differences in birth weight, gestational age at birth, congenital anomalies or infant growth as compared with baseline population data. (*21*)
Randomized control Vietnam	2013	Tdap, TT	Pregnant women: 52 received Tdap; 51 received TT	No unexpected adverse events observed following either Tdap or TT other than the expected side effects described in vaccine package insert. No significant differences in safety issues between the Tdap and TT groups. Among infants, no unexpected risk pattern or congenital disorders detected. (*22*)

Prospective cohort Australia	2015	Tdap, TIV	Pregnant women: 1,257 received only Tdap; 1,584 received only TIV; 1,506 received Tdap and TIV concomitantly	One in 10 women who received Tdap, TIV or Tdap and TIV concomitantly experienced any reaction during the week following vaccination; No difference in proportion who reported any reaction, however a significantly higher proportion who received Tdap reported experiencing swelling or pain at injection site; increase more pronounced in women who received a recent dose of Tdap. (*23*)

Abbreviations: HepB = hepatitis B vaccine; 4vHPV = human papillomavirus vaccine (quadrivalent); MMR = measles, mumps, and rubella vaccine; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Td = tetanus and diphtheria toxoids; TIV= trivalent inactivated influenza vaccine; TT= tetanus toxoid; VAR = varicella vaccine.

***** Tdap was not recommended for pregnant women until 2012.

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